The resulting filtrate is called crude extract. A batch of crude extract (minimum is a result of a full scale fermentation (target volume initiated from of the working cell bank, followed by The successive steps from which yield the crude extract are processed

C. Purification and Downstream Processing

The purification process of the crude extract, based on standard procedures, was developed with the following objectives:

- production of an enzyme having an uricolytic activity.
- elimination of process-related impurities (originating from the host strain and raw materials) (see "Impurities" Section 4.1.3).
- elimination of product - related impurities.

It consists of several and chromatography steps. The final step is filtration and filling; the resulting product is the bulk drug substance.
A batch of the drug substance is defined as that

. At the end of purification, the quantity of drug substance is about g SR29142 drug substance solution contains not less than mg of SR29142 per mL of mM

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D. Process Validation

Validation was performed to show that the drug substance production process is reproducible and robust. Equipment and facilities were qualified as well. The approach taken for process validation included verification of the consistency of several routine production runs by analysis of data collected during process monitoring, process challenge studies on selected critical parameters, and other various laboratory/pilot scale experiments. Process validation was conducted at various stages of product development. The first analysis was conducted on the results of the production of the clinical batches of drug substance after which in-depth studies were performed. Subsequently the production unit was upgraded to increase process reliability; the upgrade involved mostly facility and equipment changes but also some minor process adjustment. However, the biosynthesis of the protein was not affected because the production strain and cell bank system remain the same. While such modifications were not expected to adversely affect product characteristics, the process conducted in the upgraded facilities was subjected to complementary validation. These latter studies complete the validation program. Selected studies were presented in this section first for fermentation and extraction, then for purification to demonstrate process validation. Full documentation is available as in-house reports.

Process consistency was first evaluated during the production of several consecutive drug substance batches for clinical trials at a full [redacted] L fermentation scale. The results of these batches [redacted] are presented first for in-process controls; then additional data from supplementary in-process testing is provided to support the demonstration of consistency. The in-process control results of batches produced after the facility upgrade were provided in Section 4.3 (Vol 1.12).

Lifetime of Purification Columns and [redacted] Membranes

The process validation for defining the lifespan of the purification columns and membranes is described on pages 82-87 of vol. 1.3. This validation is based solely on an evaluation of in-process controls and is not very rigorous. The only in-process controls for [redacted] is the [redacted] after step [redacted] reveals very little regarding [redacted] in general. **(Reviewer's note: This issue was a 483 citation on the inspection)**. The lifespan for the columns has not been defined and is being established concurrent with commercial scale production.

E. Reference Standard(s)

In-house primary and working reference materials were established for SR29142 quantitative assessment. No national or international standards are available for urate oxidase. The primary reference material is a sample of drug substance produced by the process used for clinical material, which has been further purified. It is used to calibrate working reference standards as well as to verify the structure.

Working reference material are [redacted] of drug substance and drug product batches (release and stability). A preliminary working reference material prepared during process development was used initially to control the drug substance. It was replaced by the first working reference material when it became available.

Primary and working reference material

The primary reference material, batch [redacted] is used to calibrate working reference materials and to verify the structure. It was constituted in 1995.

The primary reference material was prepared from the production batch [redacted] (used for preclinical studies) stored at [redacted] C; an aliquot was further purified by the steps briefly described below.

[redacted]

- Final filtration and filling: operation conducted identically as step [redacted] of the clinical batch production process.

The resulting product, batch [redacted] was stored at [redacted] ^{0}C temporarily in a [redacted] container. It was then aliquoted in [redacted] tubes, and stored at [redacted] C. The fraction of aliquots serving to control the working reference materials was attributed the laboratory code [redacted] After dispensing, it was reanalyzed by selected tests to verify purity.

The primary reference material is considered stable under these storage conditions, as inferred from data collected calibrating the working reference material for over [redacted] years.

The primary reference material was evaluated by the drug substance release methods, and [redacted] The analytical methods employed and results are provided on pages 154-170 of Vol. 1.3.

F. Drug Substance Specifications / Analytical Methods

The specification applied to SR29142 drug substance is derived from the current Sanofi monographs [redacted] This specification was established based on data for batches of drug substance used in toxicology, clinical and stability studies including those used to demonstrate consistency. The specification for the [redacted] assure the quality as discussed below:

[redacted]

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[redacted]

Batch Analysis

The analysis of [redacted] consecutive production batchs is presented on pages 62-100 of vol. 1.4. and was found to be acceptable. The batchs analyzed were:

[redacted]

In addition, on inspection I (GJ) reviewed the actual batch records (raw data) for lots [redacted] (primary toxicology batch) and [redacted] of the batchs used in the generation of the clinical data provided in the BLA [redacted]

F. Container/Closure System for Drug Substance

The container and closure system for storage of the bulk drug substance solution is a component of the filtration and distribution system described in the purification section. The entire system was designed to allow final filtration and filling in a closed environment, and preservation of product quality until used for drug product manufacture. The [redacted] distribution system and the inner seal of the [redacted] closures for the drug substance and sample containers are manufactured as [redacted] The container and closure systems are disconnected from the rest of the system after filling by [redacted] The air vents are removed in the same manner.

G. Drug Substance Stability

The SR29142 drug substance stability consists of:

[redacted]

[redacted] batches used for clinical studies [redacted] were placed on stability for [redacted] months at [redacted] C and [redacted] months at [redacted] C to establish the expiry date for the drug substance. These were produced at [redacted] under a process practically the same as the proposed commercial one (see Section 4.3) with notably the scale unchanged. However, these data are considered supporting stability and not primary stability because of a change in the [redacted] The analytical procedures applied are the same as the ones provided for routine control and release of commercial batches. The study of these batches are the basis for the [redacted] months expiry date for the drug substance.

Overall, the results of the supporting stability at [redacted] C are as follows:

-No changes in general tests such as [redacted] observed.
-Although increases are observed for [redacted] results from [redacted] are within the acceptance criteria.
-The assay control tests are all within the acceptance criteria.

The supporting stability at the accelerated conditions of [redacted] C shows a marked deterioration of sample over time.

The **primary stability data** was on-going for [redacted] batches of drug substance produced at [redacted] y the commercial process (batchs [redacted] at the time of the BLA submission. For the first batch, the protocol includes samples stored [redacted] days to study the effect of the [redacted] on the quality of the drug substance; such contact may be met during shipping. After [redacted] days, samples were [redacted] for the remainder of the stability period. The results submitted **in the BLA** [redacted] months for one batch and [redacted] months for the other [redacted] show that changes observed are of the same nature and magnitude as those observed for the supportive stability data. In addition, the results on the [redacted] samples support the absence of a negative impact due to changes in the [redacted]

In conclusion, these results support the SR29142 expiry date of [redacted] when stored at [redacted] C in the commercial packaging configuration.

Reviewer's Note: On inspection, I (GJ) reviewed an update on the primary stability studies which demonstrated stability of drug substance for [redacted] months at [redacted] C. The sponsor will extend the stability study out to [redacted] months. One batch of drug substance per year will be submitted to their on-going stability program in the future.

III. DRUG PRODUCT

A. Composition and Specifications

The composition of drug product (BRANDNAME for Injection) to be lyophilized is:

1.50 mg/ml SR29142 (drug substance in [redacted]
15.90 mg/ml alanine [redacted]
10.60 mg/ml mannitol [redacted]
12.60-14.30 mg/ml dibasic sodium phosphate (buffer)
WFI up to 1 ml
[redacted]

Total phosphate buffer concentration is [redacted] mM and filling volume is set such that there is [redacted] mg/vial of SR29142 to ensure an extractable dose of 1.5 mg of SR29142. The industrial batch size is [redacted] liters corresponding to [redacted] vials. All excipients comply with specifications defined in the current USP-NF monographs.

The composition of the solvent for parenteral use is:

1 mg Poloxamer 188 [redacted]
WFI up to 1 ml
[redacted]

The industrial batch size is [redacted] ampoules. All excipients comply with specifications defined in the current USP-NF monographs. [redacted] is added to the poloxamer 188 to a level of [redacted] ppm. The recent USP addendum allows the use of [redacted] in poloxamer.

Drug product is reconstituted with 1 ml of solvent for parenteral use, followed by dilution into 0.9% sodium chloride up to a volume of 50 ml and administration by i.v. over 30 minutes.

B. Manufacturer(s)

The responsibilities for the manufacturing, packaging, labeling, and testing of the BRANDNAME for Injection are described below.

Name & Address	Responsibilities
Sanofi-Synthelabo [redacted]	- Identity testing of drug substance - Quality control testing of inactive components and primary packaging components - Manufacture of BRANDNAME for Injection - In-process, quality control, and microbiological testing of the BRANDNAME for Injection - Primary packaging and labeling operations - Release of labeled BRANDNAME for Injection - Shipping BRANDNAME for Injection to Abbott Laboratories - Post-approval stability studies on commercial batches
[redacted]	- Receipt of BRANDNAME for Injection - Secondary packaging[a]
Sanofi-Synthelabo [redacted]	- Receipt of BRANDNAME for Injection - Secondary packaging[b]

[a]Vials of finished labeled BRANDNAME for Injection, accompanied by a certificate of analysis, are shipped from Sanofi-Synthelabo, [redacted] be combined with the solvent for parenteral use in the finished combo pack.

[b]Vials of finished labeled BRANDNAME for Injection, accompanied by a certificate of analysis, are sbipped from Sanofi-Synthelabo, [redacted] Sanofi-Synthelabo, [redacted] to be combined with the solvent for parenteral use in the finished combo pack.

The responsibilities for the manufacturing, packaging, labeling, and testing the **solvent for parenteral use** for BRANDNAME for Injection, are described below.

Name & Address	**Responsibilities**
[redacted]	- Quality control testing of inactive components and packaging components - Manufacture of the solvent for parenteral use - In-process, quality control, and Microbiological testing of the solvent for parenteral use - Primary packaging and labeling operations - Release of finished labeled solvent for parenteral use - Post-approval stability studies on commercial batches - Secondary packaging[a]
Sanofi-Synthelabo [redacted]	- Receipt of solvent for parenteral use for BRANDNAME for Injection - Secondary packaging[b]

[a]Vials of finished labeled BRANDNAME for Injection, accompanied by a certificate of analysis, are shipped from Sanofi-Synthelabo, [redacted] to be combined with the solvent for parenteral use in the finished combo pack.

[b]Vials of finished labeled BRANDNAME for Injection, accompanied by a certificate of analysis, are shipped from Sanofi-Synthelabo, [redacted] and ampoules of finished labeled solvent for parenteral use, accompanied by a certificate of analysis, are shipped from [redacted] to Sanofi-Synthelabo, [redacted] to be combined into the finished combo pack.

C. Methods of Manufacture And Packaging

Primary packaging materials for BRANDNAME for Injection

- Clear 3 mL [redacted] glass vial
- [redacted] rubber stopper 13 mm diameter
- [redacted] cap 13 mm diameter

Operating procedure for BRANDNAME for Injection

[redacted]

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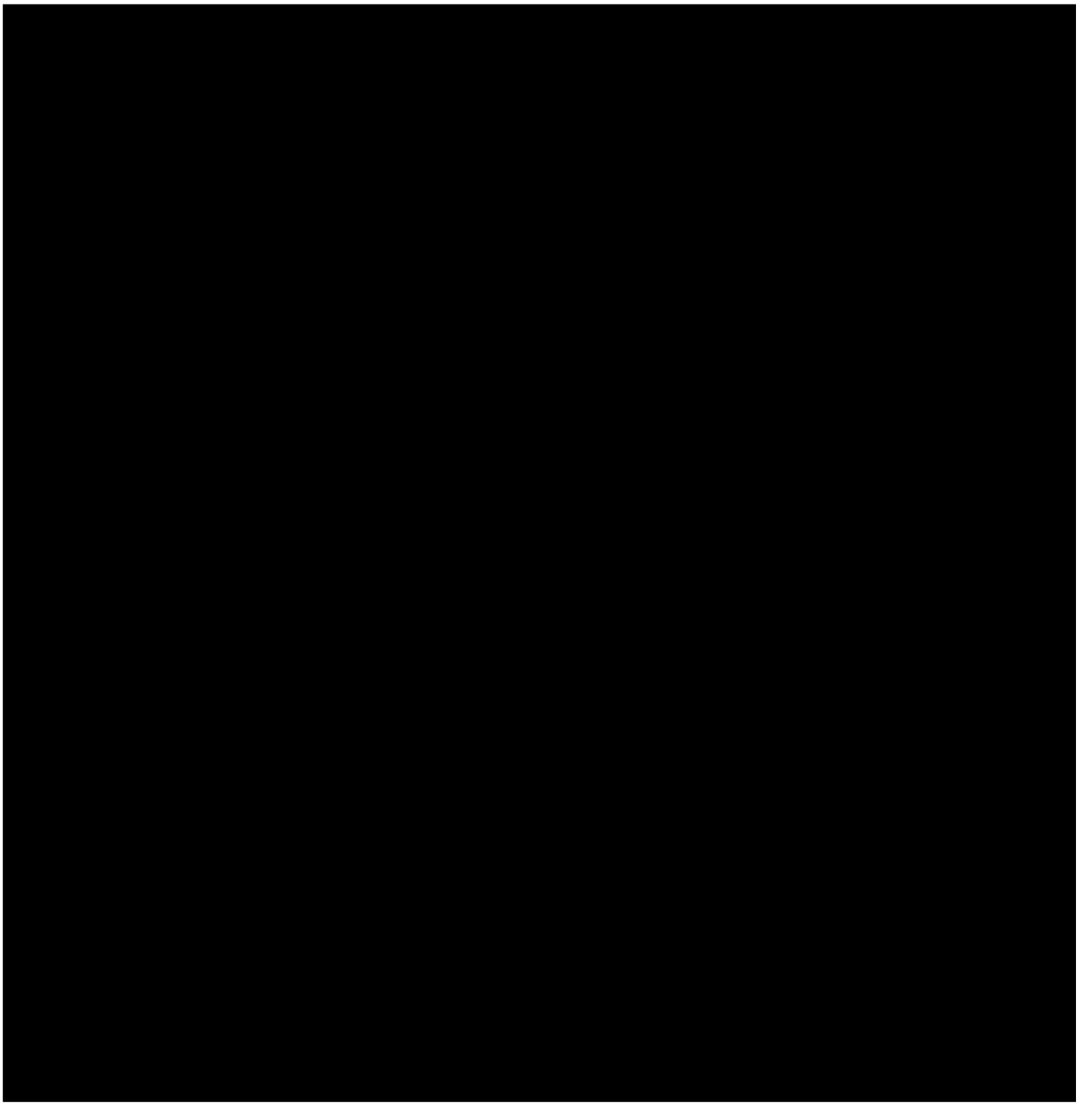

D. Release Specifications for Drug Product

Release Specifications for BRANDNAME for Injection

Control	Acceptance Criterion

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(principal peak) (mg of SR29142/vial)

Release Specifications for Solvent for Parenteral Use

Control	Acceptance Criterion
[redacted]	
Identification	
Poloxamer	[redacted]
Tests	
[redacted]	
Sterility	Meets USP<71> requirements

G. Drug Product Stability

BRANDNAME for Injection is administered intravenously as an infusion after reconstitution. It is a lyophilized powder for solution for injection (hereafter called "powder") which is reconstituted with the solvent for solution for parenteral use (hereafter called "solvent"). The reconstituted solution is then diluted for infusion with 0.9 % sodium chloride injection.

The drug product stability for the powder and the solvent consists of:

- primary stability for the powder up to 36 months on [redacted] batches [redacted] under normal and accelerated conditions to support an expiry date of 36 months at [redacted] ^{0}C. Testing was performed at [redacted] months. Assays used for this evaluation were:

[redacted]

The manufacturing procedure used to produce the primary stability powder and solvent batches and the packaging conditions for these batches are the same as that intended for commercial use.

The overall results of the stability studies conclude that:

- all results for the primary powder data comply with specification at +5 +/-3 °C up to 36 months; however the increase of related substances and related impurities at [redacted] % RH is only supported up to [redacted] months

- although the reconstituted solution is intended to be administered into man immediately, a storage of 24 hours at [redacted] °C is supported and contact with the closure does not negatively impact the solution

- typical classical infusion devices such as glass bottles, PVC bags or Intermate® systems can be readily used for the administration of the powder after reconstitution with the solvent using 0.9 % sodium chloride injection only as the infusion solution

- while the powder protected by a cardboard box, solvent, reconstituted solution and infusion solution are not sensitive to light, a prolonged exposure is not recommended

- all results for the primary solvent data comply with specification under both normal and accelerated conditions.

I. INVESTIGATIONAL PRODUCT/FORMULATION

Comparability of clinical and commercial drug substance batches

[redacted] consecutive production batches of SR29142 drug substance intended for clinical use were produced in 1994. The release control results for these batches, [redacted], were given in process validation section to demonstrate process consistency (pre-modification). After production of these batches, as the development process continued, the drug substance production site was upgraded and the process was automated to enhance process reliability. These improvements involved minor process adjustments and changes to both the facility and equipment. The biosynthesis of the protein was not affected because the production strain and cell bank system remain the same, and no significant changes were introduced to either the fermentation or the purification processes (notably, same scale and process steps, same media components, buffers and gels). Upgraded facilities and equipment have been qualified. The main process adjustments were presented on pages 1-2 of Vol. 1.12.

These differences were considered insignificant in terms of possible impact on product quality. The following batchs were prepared using the post-modification process: [redacted] Comparability between the pre-modification (clinical) batches and post-modification batches produced by the commercial process was evaluated by in-process control, release, and stability testing. In-process controls verify the consistency of the process and determine the final quality of the drug substance. The drug substance is further controlled by a comprehensive set of release tests to ensure its adequate characterization.

The in-process control and release results of [redacted] post-modification batches were on pages 5-8 of Vol 1.12. The pre-modification batch result ranges were included to facilitate comparison for drawing a conclusion on their equivalence. Also, chromatograms and gels for the actual release data were provided for the [redacted] consecutive batches presented to demonstrate consistency (commercial process validation batches) on pages 9-27 of Vol 1.12.

In conclusion, the quality of the post-modification batches is equivalent to the quality of the pre-modification batches. In addition, the post-modification results demonstrate process consistency and support process validation.